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(54) **IMPROVED METHOD FOR TREATMENT OF GASTROINTESTINAL DISORDERS.**

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(56) References cited:

EP-A- 206 626	EP-A- 0 206 625
EP-A-20 662 7	WO-A-86/05981
AU-A- 4 084 168	AU-A- 5 859 586
AU-A- 5 902 686	AU-A- 6 584 665
AU-B- 201 461	DE-A- 1 963 496
FR-A- 2 053 002	GB-A- 2 054 373

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EP 0 439 453 B1

Patent Abstracts of Japan, C-475, p. 152, JP-A-62-195329 (nippon Kayaku) 28 Aug. 1987

Antimicrobial Agents and Chemotherapy (AMACCQ), vol. 31, no. 9, Sept. 1987, Van Caekenberghe, Dirk L. et al., pp. 1429-1430

Martindale. The Extra Pharmacopoeia, 28th ed., Editor James E.F. Reynolds, pp. 927-930

Scand. J. Gast., (1991), no. 26, p. 1123-1131, Goh et al.

Gut, 1989, vol. 30, p. 1206-1212, Loffeld et al.

Gut, 1991, vol. 32, p. A1220-1221, Chiba et al.

J. Gastroenterology and Hepatology, vol. 6, 1991, p. 131-137, Axon

Irish J. of Med., no. 166, 1992, p. 6, Logan et al.

Scand. J. Gast., vol. 27, 1992, p. 281-284, Borody et al.

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Description

This invention relates to pharmaceutical compositions for eradication and/or prevention of recurrence of duodenal ulcers associated with infection by Campylobacter Pylori

C. pylori is a recently described bacterium found to cause chronic histological gastritis. Its causal role in peptic ulceration is less clear and even less so in non-ulcer dyspepsia. Its role could be more effectively studied if effective therapy for its eradication were devised.

Until recent times, C. pylori has been found to be difficult to eradicate using known chemotherapeutic agents. Although many antibiotics can suppress C. pylori growth in vitro, in vivo the mucosal concentration appears to be inadequate and penetration of the usual gastric mucus layer poor. Hence, development of an adequate in vivo eradication method for chronic C. pylori infection has been difficult. Moreover, adequate prediction of in vivo results cannot be predicted from in vitro work.

European Patent Application No. 206,625 and Australian Patent Application No. 59026/86 describe the use of bismuth together with a single antibiotic for the treatment of C. pylori. However, bismuth alone achieves low (30 to 70%) initial clearance rates for C. pylori and recurrence of the infection approaches 100% by twelve months post therapy. Bismuth together with a single antibiotic, namely amoxicillin, appears to be relatively effective as a short term means of reducing the symptoms but it is now clear that the use of bismuth together with a single antibiotic frequently fails to eradicate the infection and has a high rate of infection recurrence (Rauws, Erik A. J. et al; Gastro-enterology, 1988; 94: 33-40).

The present inventor has now found that the use of a multi antibiotic therapy not only results in a high initial clearance rate of C. pylori, of the order of greater than 90%, but also leads to a high eradication rate where most patients remain free of infection for more than twelve to eighteen months. It now seems that therapeutic success measured at eight weeks biopsy (post treatment) should be termed as clearance only whilst the term "eradication" should be used in the context of patients who remain free of C. pylori infection for more than twelve months post treatment.

The present inventor has also found that C. pylori is not only associated with gastritis but is also causally associated with peptic ulcer including duodenal, pre-pyloric, gastric, oesophageal and marginal ulcer. The compositions for eradication of C. pylori described in the present invention are useful in the treatment of duodenal ulcers.

In one broad form the present invention provides a pharmaceutical composition for the treatment of duodenal ulcers associated with C. pylori infections comprising a pharmaceutically acceptable bismuth compound, a first antibiotic or antimicrobial agent selected from one or more of tetracyclines, penicillins, cephalosporins, furazolidones, lincosamides, nitrofurantoins and/or polypeptides and a second antibiotic or antimicrobial agent selected from one or more of quinolones, furazolidones, and/or, metronidazoles,.

The invention also provides a sequential pack for the administration of at least two pharmaceutical compositions comprising a first composition which comprises a pharmaceutically acceptable bismuth compound, a first antibiotic or antimicrobial agent selected from one or more of tetracyclines, penicillins, cephalosporins, furazolidones, lincosamides, nitrofurantoins and/or polypeptides and a second antibiotic or antimicrobial agent, selected from one or more of quinolones, furazolidones, and/or, metronidazoles, in unit dosage form adapted and presented for a first administration period of 3 to 36 days, together with a second pharmaceutical composition which comprises an acid suppressant for ulcer treatment in unit dosage form adapted and presented for a second administration period of 3 to 36 days prior to or overlapping with the initial part of said first administration period.

Preferably the first antibiotic or antimicrobial agent is selected from tetracyclines and/or penicillins and the second antibiotic is a metronidazole.

The tetracyclines include tetracycline, oxytetracycline, doxycycline, demeclocycline, methacycline and minocycline.

The penicillins include penicillin G, penicillin V, oxacillin, nafcillin, ampicillin, amoxicillin, cloxacillin and carbenicillin.

The metronidazoles include metronidazole and tinidazole.

Rifanpin, trimethoprim and/or nalidixic acid may also be used.

The cephalosporins include cephalexin (Keflex®), cefaclor, cephapirin, cephradine and cefadroxil as well as second and third generation cephalosporins.

The polypeptide antibiotics include polymyxin B, bacitracin, colisin sulfate and/or spectinomycin HCl.

Quinolones include ciprofloxacin, norfloxacin and ofloxacin.

Lincosamides include lincomycin and clindamycin.

A third or more antibiotics may be included in the methodology and compositions of the invention; eg amoxicillin, tetracycline and metronidazole. Keflex® is also preferably used as the first antibiotic or as a

further antibiotic.

Bismuth compounds suitable in the present invention include those selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate, and mixtures thereof. Bismuth citrate, bismuth subcitrate, tripotassium dicitrato bismuthate. bismuth tartrate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention. The bismuth useful herein may be administered alone, or in combination with other pharmaceutically-acceptable components, in a bismuth-containing composition. A variety of such compositions containing bismuth salts are commercially available, including, for example, DeNol®, containing tripotassium dicitrato bismuthate (sold by Gist-Brocades N.V.), Noralac®, containing bismuth aluminate, alginic acid, and magnesium carbonate (manufactured by North American Pharmaceuticals), Roter bismuth, containing bismuth subnitrate (sold by Roter Laboratories), Fensobar® Polvo, containing bismuth subcarbonate among other materials (manufactured by USV Pharmaceutical Corporation), and Pepto-Bismol®, containing bismuth subsalicylate (sold by The Procter & Gamble Company).

In a aspect of the present invention there is provided a capsule for oral administration to patients suffering from duodenal ulcers associated with C. pylori wherein said capsule includes a pharmaceutically acceptable bismuth compound together with a first antibiotic and a second antibiotic wherein said capsule is adapted to release said bismuth within the stomach of the recipient and wherein at least said first antibiotic and preferably also said second antibiotic is microencapsulated so that said first and optionally said second antibiotic is released within the gastro intestinal tract after said stomach.

In a preferred form of this aspect of the invention there is provided a capsule containing an effective amount of a pharmaceutically acceptable bismuth compound together with enteric coated micro-spherules of an antibiotic of the tetracycline class or penicillin class which capsule also contains an effective amount of a second antibiotic selected from the metronidazole class which second antibiotic is optionally provided in enteric coated micro-spherule form.

In a further aspect of the present invention the methodology uses the treatment regimen comprising the combination of pharmaceutically acceptable bismuth compound in combination with a first antibiotic and a second antibiotic for between three to twenty-eight days. Preferably the treatment is combined with the administration of an acid suppressant such as an histamine$_2$ antagonist such as cimetidine, ranitidine or famotidine to effect symptomatic relief and ulcer epithelialization. This is followed by the combination of the bismuth and first and second antibiotic therapy. Preferably the histamine$_2$ antagonist is administered for three to twenty-eight days followed by a three to twenty-eight day therapy of the bismuth/antibiotics combination. Other acid suppressants may be used instead of an histamine$_2$ antagonist such as benzimidazole or prostoglandins. Alternatively, the histamine$_2$ blocker or other acid suppressant can be combined with the pharmaceutical composition of the present invention.

The present invention also provides a sequence presented pack suitable for therapy for duodenal ulcers associated with C. pylori infection which combines a pharmaceutically acceptable bismuth compound together with a first antibiotic and a second antibiotic and optionally further antibiotics so that said treatment regimen can be adapted for individual patient needs. Optionally the sequence presented pack may also include an initial therapy comprising an acid suppressant such as a histamine$_2$ antagonist or a K/Na ATP-ase inhibitor such as omeprazole and may be combined with mucus disrupting agents such as carbocysteine, n-acetylcysteine, corticosteroids or bisolvon® (bromhexine). It should be noted that the pharmaceutical composition comprises at least two antibiotics but further antibiotics may be selectively added in difficult cases or where resistant strains and/or multiple strains present a more resistant problem.

In the composition of the present invention, preferably from 5 to 5000mg, more preferably 50 to 250mg of a pharmaceutically acceptable bismuth compound is used together with from 5 to 10000mg, more preferably 50 to 500mg of a first antibiotic together with from 5 to 10000mg, more preferably 50 to 250mg of a second antibiotic.

Preferably the invention provides a pharmaceutical composition containing from 50 to 250mg of a colloidal bismuth in pharmaceutically acceptable form, 50 to 500mg of tetracycline or a penicillin (eg amoxicillin) type antibiotic and 50 to 250mg of a metronidazole type antibiotic such as metronidazole or tinidazole. Preferably the tetracycline or penicillin is microencapsulated to prevent bismuth chelation at high pH.

In a further aspect the invention provides a sequential pack comprising an antimicrobial pharmaceutical composition in unit dosage form adapted for an administration period of three to thirty-six days, said antimicrobial composition comprising a pharmaceutically acceptable bismuth compound, at least a first antibiotic and at least a second antibiotic, together with a palliative pharmaceutical composition in unit dosage form adapted and presented for a three to thirty-six day administration period prior to, or

overlapping with the initial part of the administration period of said antimicrobial pharmaceutical composition wherein said palliative pharmaceutical composition comprises a therapeutic agent such as an acid suppressant, adapted for ulcer treatments.

In a further aspect the invention provides a sequential pack comprising a first pharmaceutical composition in unit dosage form adapted for an administration period of three to thirty six days, said composition comprising a pharmaceutically acceptable bismuth compound and at least a first antibiotic, together with a second pharmaceutical composition in unit dosage form comprising a second antibiotic adapted for administration for a period different to said administration period of said first pharmaceutical composition. Preferably the pack further comprises a palliative pharmaceutical composition in unit dosage form presented in said pack in a 3 to 36 day administration period which is prior to or overlaps with the initial part of the administration period of said first pharmaceutical composition wherein said palliative pharmaceutical composition comprises a therapeutic agent, such as an acid suppressant, adapted for ulcer treatment.

The compositions described above are useful in the treatment of duodenal ulcers associated with C. pylori.

Whilst tablets or capsules of the pharmaceutical composition of the present invention are preferred, sachets or syrups or other orally ingestible forms of the compositions are also included within the scope of the present invention.

The invention will be further described with reference to the following test procedure of the Example and accompanying Figures wherein Figure 1 shows the results of treatment of the present invention in 64 out of 100 patients at an average of 19.3 months post treatment and Figure 2 shows the histologic grading pre and post treatment with the treatment of the present invention.

EXAMPLE

Test Procedure

Patients aged 19 to 79 years (M:F = 47:53) with symptoms of dyspepsia lasting three months or more referred for endoscopy, were entered. Only patients positive for C. pylori with either duodenal ulcer or non-ulcer dyspepsia were entered into the study. Patients were deemed to have non-ulcer dyspepsia if, in the absence of ulcer or other disease, they complained of food related epigastric discomfort or pain, bloating, belching, nausea, a feeling of fullness or heartburn. Patients with duodenal ulcer were entered into the treatment protocol only after ulcer treatment with either four weeks of ranitidine (300mg/day) or cimetidine (800mg/day), known not to influence C. pylori. Exclusion criteria included coagulopathy, antibiotic use within two weeks of endoscopy, presence of oesophageal varices, previous gastrectomy, neoplasm, systemic disease or allergy preventing use of the medications. Gastric ulcer patients were excluded to form a separate study. Of 122 patients entered in the study, 112 completed the triple chemotherapy adequately. Of these, 100 consecutive re-endoscoped patients became available for analysis of results at eight weeks after commencement of treatment and constitutes the short term follow up group. Ten patients did not complete the treatment due to failure to follow up (4), nausea (2), clostridium difficile-positive diarrhoea (1), allergy (2), and oral moniliasis (1). At 12 to 37 months after C. pylori eradication therapy CP-negative patients at eight weeks from the pilot studies and the abovementioned group were invited for re-examination by gastroscopy. Of the entire cohort 64 patients returned for examination and constitute the long term follow up group.

Gastroscopy

All examinations were carried out by the same endoscopist. Two biopsy specimens were taken from the gastric antrum and one from the body. One antral specimen was placed in a microtitre tray containing buffered urea and an indicator to detect rapidly presence of C. pylori urease activity. The other specimens were placed in 10% buffered formalin for histological examination. No bacterial cultures were carried out.

Histological Assessment

Paraffin sections of tissues fixed in formalin were stained with haematoxylin and eosin to grade severity of histological gastritis and with Warthin-Starry silver stain to grade C. pylori density. Grading was based on density of lymphocyte/plasma cell (chronic), neutrophil (active) infiltration, or presence of C. pylori from O to III as previously described.

Specimens were graded by the same consultant histopathologist without knowledge of patients' details.

Medication

Except for eight patients allergic to tetracycline, all subjects received a combination of colloid bismuth substrate (108mg chew-tablets q.i.d.), tetracycline HCl (500mg q.i.d.) for four weeks, together with metronidazole (200mg q.i.d.) for the first ten days. Amoxicillin (500mg q.i.d.) was substituted for tetracycline in the eight allergic patients. Patients and endoscopist were not blinded to the treatment regimen. Patients were asked if they had completed the medication as requested but no tablet count was attempted.

Assessment of Symptoms

For patients with idiopathic non-ulcer dyspepsia (NUD) a questionnaire form was developed and administered six months following clearance of C. pylori. Global assessment of percent improvement in these patients is reported below. In duodenal ulcer patients symptom improvement or disappearance was recorded.

RESULTS

Clearance of C. Pylori at eight weeks

Of the 100 consecutive available patients treated for C. pylori, 94 were negative on urease testing and histology at eight weeks after commencement of chemotherapy (See Table 1). The six patients remaining positive at eight weeks claimed to have taken their medication as directed.

Long Term Clearance of C. pylori

Follow up gastroscopic biopsies were obtained in 64 patients (M:F = 36:28) at 12 to 37 months after original triple chemotherapy (mean = 19.3 months), and results shown in Fig. 1 . These patients were drawn from the 94 who remained CP negative at eight weeks post therapy and from a small pilot study carried out some months earlier. Of these 64, paid recalled volunteers who resubmitted to gastroscopic biopsy, 33 had been originally diagnosed as having non-ulcer dyspepsia while 28 had endoscopically-proven duodenal ulcer. At follow up overall 60 or 94% remained free of C. pylori infection at the 19.3 months. One of the 33 NUD patients was again positive for the bacteria while three of 31 patients originally with duodenal ulcer were CP positive. In the latter three patients, two again had re-ulcerated while the other patient had pronounced duodenitis. All 28 patients who remained free of C. pylori maintained their ulcers endoscopically healed. They were on no maintenance therapy and were free of ulcer-like symptoms.

In NUD patients, as a global assessment in the 32 cleared patients, 25/32 (78%) reported a "50% or more improvement" over their initial symptom scores. On the other hand in four other patients with NUD in spite of CP eradication and reversal of histologic gastritis no improvement in dyspeptic symptoms occurred.

An unexpected finding in four of 15 patients who initially had linear oesophageal ulceration, was total healing and disappearance of the ulcers after C. pylori eradication. No appreciable weight change had occurred in these patients and the improvement could not be ascribed to any other medical therapy.

Table 1

Patient		Age	M/F	*C. pylori* at start of treatment	*C. pylori* 8wks past therapy
1	N.U.D	65	F	+ve	-ve
2	D.U	59	M	+ve	-ve
3	N.U.D	62	F	+ve	-ve
4	N.U.D	63	M	+ve	-ve
5	N.U.D	35	M	+ve	-ve
6	P.P.U	74	F	+ve	-ve
7	G.U 3	40	F	+ve	+ve*
8	D.U	65	M	+ve	-ve
9	2 D.U	55	F	+ve	-ve
10	D.U	60	M	+ve	+ve*
11	N.U.D	60	M	+ve	-ve
12	N.U.D	66	M	+ve	-ve
13	P.P.U	59	M	+ve	-ve
14	N.U.D	28	F	+ve	-ve
15	P.P.U	36	M	+ve	-ve
16	D.U	22	M	+ve	-ve
17	D.U	42	F	+ve	-ve
18	N.U.D	65	F	+ve	-ve
19	D.U	32	M	+ve	-ve
20	D.U	65	M	+ve	-ve
21	N.U.D	61	M	+ve	-ve
22	D.U	29	F	+ve	+ve*
23	N.U.D	29	M	+ve	-ve
24	N.U.D	30	M	+ve	-ve
25	D.U	74	M	+ve	-ve
26	N.U.D	42	M	+ve	-ve
27	N.U.D	38	M	+ve	+ve*
28	P.P.U	51	F	+ve	-ve
29	N.U.D	26	M	+ve	-ve

Table 1 cont'd

Patient		Age	M/F	C. pylori at start of treatment	C. pylori 8wks past therapy
30	D.U	44	F	+ve	-ve
31	D.U	50	M	+ve	-ve
32	N.U.D	29	F	+ve	-ve
33	N.U.D	72	F	+ve	-ve
34	N.U.D	29	M	+ve	-ve
35	N.U.D	22	F	+ve	-ve
36	D.U	28	M	+ve	-ve
37	D.U	54	M	+ve	-ve
38	N.U.D	44	F	+ve	-ve
39	N.U.D	56	F	+ve	-ve
40	N.U.D	40	M	+ve	-ve
41	N.U.D		M	+ve	-ve
42	N.U.D	65	F	+ve	-ve
43	G.U/D.U	53	F	+ve	-ve
44	N.U.D	43	M	+ve	-ve
45	N.U.D	73	F	+ve	-ve
46	N.U.D		F	+ve	-ve
47	N.U.D	46	F	+ve	-ve
48	N.U.D	41	M	+ve	-ve
49	N.U.D	46	F	+ve	-ve
50	N.U.D	34	M	+ve	-ve
51	N.U.D	58	F	+ve	-ve
52	N.U.D	51	F	+ve	-ve
53	N.U.D	23	M	+ve	-ve
54	N.U.D	54	F	+ve	-ve
55	D.U	59	F	+ve	-ve
56	P.P.U	31	M	+ve	-ve
57	O.U	56	M	+ve	-ve
58	N.U.D	33	M	+ve	-ve
59	PREV G.U	78	M	+ve	-ve
60	N.U.D	63	M	+ve	-ve
61	N.U.D	27	M	+ve	-ve
62	N.U.D	45	F	+ve	-ve
63	N.U.D	38	M	+ve	-ve
64	N.U.D	36	M	+ve	-ve

Table 1 cont'd

Patient		Age	M/F	C. pylori at start of treatment	C. pylori 8wks past therapy
65	N.U.D	66	F	+ve	-ve
66	N.U.D	70	F	+ve	-ve
67	P.P.U	66	F	+ve	-ve
68	D.U	37	F	+ve	-ve
69	N.U.D	64	M	+ve	-ve
70	N.U.D	45	M	+ve	-ve
71	N.U.D	24	F	+ve	-ve
72	N.U.D	46	M	+ve	-ve
73	N.U.D	53	F	+ve	-ve
74	N.U.D	33	M	+ve	-ve
75	N.U.D	30	M	+ve	-ve
76	N.U.D	42	F	+ve	-ve
77	D.U	36	M	+ve	-ve
78	N.U.D	64	F	+ve	-ve
79	D.U	34	M	+ve	-ve
80	N.U.D	65	F	+ve	-ve
81	N.U.D	56	M	+ve	+ve*
82	N.U.D	42	M	+ve	-ve
83	N.U.D	43	F	+ve	-ve
84	N.U.D	75	F	+ve	-ve
85	N.U.D	62	F	+ve	-ve
86	N.U.D	64	F	+ve	-ve
87	N.U.D	51	M	+ve	-ve
88	N.U.D	39	M	+ve	-ve
89	N.U.D	39	F	+ve	-ve
90	N.U.D	40	M	+ve	-ve
91	N.U.D	34	F	+ve	-ve
92	N.U.D	60	M	+ve	-ve
93	N.U.D	59	M	+ve	-ve
94	N.U.D	67	M	+ve	-ve
95	N.U.D	60	F	+ve	-ve
96	N.U.D	38	M	+ve	-ve
97	N.U.D	53	M	+ve	+ve*
98	N.U.D	51	M	+ve	-ve
99	N.U.D	54	M	+ve	-ve

Table 1 cont'd

Patient	Age	M/F	C. pylori at start of treatment	C. pylori 8wks past therapy
100 N.U.D	56	M	+ve	-ve

* indicates failure to cure infection.

D.U = Duodenal ulcer
O.U = Oesophageal ulcer
P.P.U = Pre-pyloric ulcer
G.U = Gastric ulcer
N.U.D = Non-ulcer dyspepsia

Histological Changes

The effects of therapy on histological grading of C. pylori density as well as lymphocyte and neutrophil infiltration are summarized in Figure 2.

Histological scores have been arbitrarily assigned to show graphically the time-course of inflammation resolution. All patients presented initially with high scores for both chronic and active gastritis. Neutrophil infiltration disappeared rapidly parallelling C./pylori clearance. Lymphocyte infiltration, on the other hand, persisted for a much longer time.

This study has demonstrated that high (> 90%) initial "clearance" of gastric C. pylori is possible with a combination of available antimicrobial agents. Such a high level of initial clearance has not been previously achieved. It is also clear that therapeutic success measured at the eight week biopsy, should for the present be termed "clearance". The term "eradication" should be reserved for patients remaining free of CP beyond six months. In this study most of those patients cleared of CP at eight weeks remained clear of the infection for more than twelve months.

Although C. pylori is susceptible to numerous antibiotics in vitro, such agents notoriously fail to eradicate it in vivo. Bismuth appears to be an important component in the combination chemotherapy. While it is not clear why several antimicrobials are required to improve eradication of CP, antibiotic access to the bacteria may be a problem. The bismuth compound may be required locally within the gastric pits and mucus whereas the antibiotics could be required to be carried systemically to reach bacteria deep in gastric pits and within endocytotic vacuoles. Presence of multiple strains of C. pylori with varying antibiotic susceptibility spectra could provide another explanation for the need to employ multiple antibiotics. In view of the multiplicity of strains, it is in fact surprising that such a high CP clearance rate could be achieved employing only two systemic antimicrobials and one locally-acting agent (CBS). Perhaps the success can be further explained by prevention of the development of resistant strains seen after short courses of single systemic antibiotics.

A clinically useful method for successful long term C. pylori eradication has not previously been described. Twelve month follow up figures of 51% and 35% have been reported using bismuth plus a single antibiotic. Such therapy would clearly be unsatisfactory for patients and may lead to creation of resistant C. pylori strains. It is also desirable to have an effective eradication therapy for C. pylori before embarking upon a double-blind trial designed to demonstrate the relevance of the organism in a particular disease.

Although it is known that bismuth can decrease tetracycline bioavailability, the antibiotic combination as used here achieved its desired effect in spite of presumed chelation. It would appear that adequate bismuth and tetracycline remained post-chelation to reach the infected targets. It is known also that chelation is in part pH dependent and low pH protects against chelation. As some patients with C. pylori infection will have impaired gastric acid secretion, elevated pH may have contributed to treatment failures. Other sources of treatment failure could include reduction in tetracycline bioavailability by ingestion of milk, antacids, iron or food, or simply non-compliance.

Claims

1. Use in the manufacture of a medicament for the eradication and/or prevention of duodenal ulcers associated with Campylobacter pylori infections of a combination of a pharmaceutically acceptable bismuth compound, a first antibiotic or antibacterial agent selected from one or more of tetracyclines, penicillins, cephalosporins, furasolidones, lincosamides, nitrofurantoins, and/or polypeptides and a second antibiotic or antibacterial agent selected from the one or more of quinolones, furazolidones and/or metronidazoles.

2. Use according to claim 1, wherein said bismuth compound is selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, colloidal bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate, and mixtures thereof.

3. Use according to claim 1 or 2, wherein said first antibiotic or antibacterial agent is a penicillin or tetracycline.

4. Use according to claim 1, 2 or 3, wherein said second antibiotic or antibacterial agent is metronidazole.

5. Use according to any one of claims 1 to 4 the combination further comprises a third antibiotic or antibacterial agent.

6. Use according to any one of claims 1 to 5 wherein the combination further comprises an acid suppressant for ulcer treatment in the presence of any antibiotic or antibacterial agent.

7. Use according to claim 6, wherein said acid suppressant is a histamine$_2$ antagonist or a K/Na ATP-ase inhibitor.

8. Use according to claim 7, wherein said histamine$_2$ antagonist is a cimetidine, ranitidine or famotidine or a benzimidazole or prostaglandin or said K/Na ATP-ase inhibitor is omeprazole.

9. Use according to any one of claims 1 to 8, wherein the combination further comprises a mucus disrupting agent.

10. Use according to claim 9, wherein said mucus disrupting agent is carbocysteine, N-acetylcysteine, a corticosteroid or bromhexine.

11. A pharmaceutical composition for the eradication and/or prevention of duodenal ulcers associated with C.pylori infections, comprising a pharmaceutically acceptable bismuth compound, a first antibiotic or antibacterial agent selected from one or more of tetracyclines, penicillins, cephalosporins, furazolidones, lincosamides, nitrofurantoins, and/or polypeptides and a second antibiotic or antibacterial agent selected from the one or more of quinolones, furazolidones and/or metronidazoles.

12. The composition of claim 11, wherein said bismuth compound is selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, colloidal bismuth subcitrate, bismuth citrate,tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate, and mixtures thereof.

13. The composition of claim 11 or 12, wherein said first antibiotic or antibacterial agent is a penicillin or tetracycline.

14. The composition of claim 11, 12 or 13, wherein said second antibiotic or antibacterial agent is metronidazole.

15. The composition of any one of claims 11 to 14 wherein the combination further comprises a mucus disrupting agent.

16. The composition of claim 15 wherein said mucus disrupting agent is carbocysteine, N-acetylcysteine, a corticosteroid or bromhexine.

17. The composition of any one of claims 11 to 16, which further comprises a therapeutically effective amount of an acid suppressant for ulcer treatment in the presence of any antibiotic or antibacterial agent.

18. The composition of claim 17 wherein said acid suppressant is a histamine$_2$ antagonist or a K/Na ATP-ase inhibitor.

19. The composition of claim 18 wherein said histamine$_2$ antagonist is a cimetidine, ranitidine or famotidine or a bensimidazole or prostaglandin or said K/Na ATP-ase inhibitor is omeprazole.

20. A composition according to any one of claims 17 to 19 in the form of a sequential pack comprising a first pharmaceutical composition in unit dosage form adapted and presented for a first administration period of 3 to 36 days comprising the pharmaceutically acceptable bismuth compound and the said first and second antibiotic or antibacterial agents, and a second pharmaceutical composition comprising the said acid suppressant for ulcer treatment in unit dosage form adapted and presented for a second administration period of 3 to 36 days prior to, or overlapping the initial part of, the said first administration period.

Patentansprüche

1. Verwendung einer Kombination aus einer pharmazeutisch annehmbaren Bismutverbindung, einem ersten antibiotischen oder antibakteriellen Mittel, das aus einem oder mehreren Tetracyclinen, Penicillinen, Cephalosporinen, Lincosamiden, Nitrofurantoinen und/oder Polypeptiden ausgewählt ist, und einem zweiten antibiotischen oder antibakteriellen Mittel, das aus einem oder mehreren Chinolinen, Furazolidonen und/oder Metronidazolen ausgewählt ist, bei der Herstellung eines Arzneimittels zur Entfernung und/oder Verhütung von Zwölffingerdarmgeschwüren, die mit Campylobacter pylori-Infektionen zusammenhängen.

2. Verwendung gemäß Anspruch 1, bei welcher die Bismutverbindung aus Bismutaluminat, Bismutsubcarbonat, Bismutsubcitrat, kolloidalem Bismutsubcitrat, Bismutcitrat, Trikaliumdicitratobismutat, Bismutsubgallat, Bismutsubnitrat, Bismuttartrat, Bismutsalicylat, Bismutsubsalicylat und deren Gemischen ausgewählt ist.

3. Verwendung gemaß Anspruch 1 oder 2, bei welcher das erste antibiotische oder antibakterielle Mittel ein Penicillin oder Tetracyclin ist.

4. Verwendung gemäß Anspruch 1, 2 oder 3, bei welcher das zweite antibiotische oder antibakterielle Mittel Metronidazol ist.

5. Verwendung gemäß einem der Ansprüche 1 bis 4, wobei die Kombination weiter ein drittes antibiotisches oder antibakterielles Mittel enthält.

6. Verwendung gemäß einem der Ansprüche 1 bis 5, wobei die Kombination weiter ein säurehemmendes Mittel zur Ulkusbehandlung in Gegenwart eines antibiotischen oder antibakteriellen Mittels enthält.

7. Verwendung gemäß Anspruch 6, bei welcher das säurehemmende Mittel ein Histamin$_2$-Antagonist oder ein K/Na-ATPase-Hemmer ist.

8. Verwendung gemaß Anspruch 7, bei welcher der Histamin$_2$-Antagonist Cimetidin, Ranitidin oder Famotidin oder ein Benzimidazol oder Prostaglandin ist oder der K/Na-ATPase-Hemmer Omeprazol ist.

9. Verwendung gemäß einem der Ansprüche 1 bis 8, bei welcher die Kombination weiter ein schleimlösendes Mittel enthält.

10. Verwendung gemäß Anspruch 9, bei welcher das schleimlösende Mittel Carbocystein, N-Acetylcystein, ein Corticosteroid oder Bromhexin ist.

11. Pharmazeutische Zusammensetzung zur Entfernung und/oder Verhütung von Zwölffingerdarmgeschwüren, die mit C. pylori-Infektionen zusammenhängen, umfassend eine pharmazeutisch annehmbare Bismutverbindung, ein erstes antibiotisches oder antibakterielles Mittel, das aus einem oder mehreren Tetracyclinen, Penicillinen, Cephalosporinen, Lincosamiden, Nitrofurantoinen und/oder Polypeptiden ausgewählt ist, und ein zweites antibiotisches oder antibakterielles Mittel, das aus einem oder mehreren Chinolinen, Furazolidonen und/oder Metronidazolen ausgewählt ist.

12. Zusammensetzung des Anspruchs 11, in welcher die Bismutverbindung aus Bismutaluminat, Bismutsubcarbonat, Bismutsubcitrat, kolloidalem Bismutsubcitrat, Bismutcitrat, Trikaliumdicitratobismutat, Bismutsubgallat, Bismutsubnitrat, Bismuttartrat, Bismutsalicylat, Bismutsubsalicylat und deren Gemischen ausgewählt ist.

13. Zusammensetzung des Anspruchs 11 oder 12, in welcher das erste antibiotische oder antibakterielle Mittel ein Penicillin oder Tetracyclin ist.

14. Zusammensetzung des Anspruchs 11, 12 oder 13, in welcher das zweite antibiotische oder antibakterielle Mittel Metronidazol ist.

15. Zusammensetzung eines der Ansprüche 11 bis 14, in welcher die Kombination weiter ein schleimlösendes Mittel enthält.

16. Zusammensetzung des Anspruchs 15, in welcher das schleimlösende Mittel Carbocystein, N-Acetylcystein, ein Corticosteroid oder Bromhexin ist.

17. Zusammensetzung eines der Ansprüche 11 bis 16, welche weiter eine therapeutisch wirksame Menge eines säurehemmenden Mittels zur Ulkusbehandlung in Gegenwart eines antibiotischen oder antibakteriellen Mittels enthält.

18. Zusammensetzung des Anspruchs 17, in welcher das säurehemmende Mittel ein Histamin$_2$-Antagonist oder ein K/Na-ATPase-Hemmer ist.

19. Zusammensetzung des Anspruchs 18, in welcher der Histamin$_2$-Antagonist Cimetidin, Ranitidin oder Famotidin oder ein Benzimidazol oder Prostaglandin ist oder der K/Na-ATPase-Hemmer Omeprazol ist.

20. Zusammensetzung gemäß einem der Ansprüche 17 bis 19 in Form einer Sequentialpackung, umfassend eine erste pharmazeutische Zusammensetzung in Einzeldosisform, welche für einen ersten Verabreichungszeitraum von 3 bis 36 Tagen dargeboten wird und daran angepaßt ist und welche die pharmazeutisch annehmbare Bismutverbindung und das erste und zweite antibiotische oder antibakterielle Mittel umfaßt, und eine zweite pharmazeutische Zusammensetzung, welche das säurehemmende Mittel zur Ulkusbehandlung in Einzeldosisform umfaßt, welche für einen zweiten Verabreichungszeitraum von 3 bis 36 Tagen vor dem ersten Verabreichungszeitraum dargeboten wird und daran angepaßt ist oder sich mit dessen anfänglichem Teil überlappt.

Revendications

1. Utilisation pour la préparation d'un médicament pour l'éradication et/ou la prévention des ulcères duodénaux associés aux infections par Campylobacter pylori, d'une combinaison de composés de bismuth pharmaceutiquement acceptables, d'un premier antibiotique ou agent antibactérien choisi parmi un ou plusieurs composants du groupe formé des tétracyclines, des pénicillines, des céphalosporines, des lincosamides, des nitrofurantoïnes et/ou des popypeptides et d'un deuxième antibiotique ou agent antibactérien choisi parmi un ou plusieurs composants du groupe formé des quinolones, des furazolidones et/ou des métronidazoles.

2. Utilisation selon la revendication 1, dans laquelle ledit composé de bismuth est choisi parmi le groupe formé de l'aluminate de bismuth, du sous-carbonate de bismuth, du sous-citrate de bismuth, du sous-

citrate de bismuth colloïdal, du citrate de bismuth, du dicitratobismuthate tripotassique, du sous-gallate de bismuth, du sous-nitrate de bismuth, du tartrate de bismuth, du salicylate de bismuth, du sous-salicylate de bismuth et des mélanges de ceux-ci.

3. Utilisation selon la revendication 1 ou 3, dans laquelle ledit premier antibiotique ou agent antibactérien est une pénicilline ou une tétracycline.

4. Utilisation selon la revendication 1, 2 ou 3, dans laquelle ledit deuxième antibiotique ou agent antibactérien est le métronidazole.

5. Utilisation selon l'une quelconque des revendications 1 à 4, la combinaison comprenant en outre un troisième antibiotique ou agent antibactérien.

6. Utilisation selon l'une quelconque des revendications 1 à 5, dans laquelle la combinaison comprend en outre un suppresseur d'acide pour le traitement de l'ulcère en présence de n'importe quel antibiotique ou agent antibactérien.

7. Utilisation selon la revendication 6 dans laquelle ledit suppresseur d'acide est un antagoniste de l'histamine 2 ou un inhibiteur du K/Na ATP-ase.

8. Utilisation selon la revendication 7 dans laquelle ledit antagoniste de l'histamine 2 est la cimétidine, la ranitidine ou la famotidine ou un benzimidazole ou la prostaglandine ou ledit inhibiteur du K/Na ATP-ase est l'oméprazole.

9. Utilisation selon l'une quelconque des revendications 1 à 8, dans laquelle la combinaison comprend, en outre, un agent de désintégration du mucus.

10. Utilisation selon la revendication 9, dans laquelle ledit agent de désintégration du mucus est la carbocystéine, la N-acétylcystéine, un corticostéroïde ou la bromhexine.

11. Composition pharmaceutique pour l'éradication et/ou la prévention des ulcères duodénaux associés aux infections par C. pylori, comprenant un composé de bismuth pharmaceutiquement acceptable, un premier antibiotique ou agent antibactérien choisi parmi un ou plusieurs des constituants du groupe formé des tétracyclines, des pénicillines, des céphalosporines, des lymcosamies, des nitrofurantoïnes et/ou des polypeptides et d'un deuxième antibiotique ou agent antibactérien choisi parmi un ou plusieurs des constituants du groupe formé des quinolones, des furazolidones et/ou des métronidazoles.

12. Composition selon la revendication 11, dans laquelle ledit composé de bismuth est choisi parmi le groupe formé de l'aluminate de bismuth, du sous-carbonate de bismuth, du sous-citrate de bismuth, du sous-citrate de bismuth colloïdal, du citrate de bismuth, du dicitratobismuthate tripotassique, du sous-gallate de bismuth, du sous-nitrate de bismuth, du tartrate de bismuth, du salicylate de bismuth, du sous-saliicylate de bismuth et des mélanges de ceux-ci.

13. Composition selon la revendication 11 ou 12, dans laquelle ledit premier antibiotique ou agent antibactérien est une pénicilline ou une tétracycline.

14. Composition selon la revendication 11, 12 ou 13, dans laquelle ledit deuxième antibiotique ou agent antibactérien est le métronidazole.

15. Composition selon l'une quelconque des revendications 11 à 14, dans laquelle la combinaison comprend, en outre, un agent de désintégration du mucus.

16. Composition selon la revendication 15, dans laquelle ledit agent de désintégration du mucus est la carbocystéine, la N-acétylcystéine, un corticostéroïde ou la bromhexine.

17. Composition selon l'une quelconque des revendications 11 à 16, comprenant en outre une quantité thérapeutiquement efficace d'un suppresseur d'acide pour le traitement de l'ulcère en présence de tout

antibiotique ou agent antibactérien.

18. Composition selon la revendication 17, dans laquelle ledit suppresseur d'acide est un antagoniste de l'histamine 2 ou un inhibiteur de K/Na ATP-ase.

19. Composition selon la revendication 18, dans laquelle ledit antagosniste de l'histamine 2 est la cimétidine, la ranitidine ou la famotidine ou un benzimidazole ou la prostaglandine ou ledit inhibiteur de K/Na ATP-ase est l'oméprazole.

20. Composition selon l'une quelconque des revendications 17 à 19, sous forme d'un ensemble séquentiel comprenant une première composition pharmaceutique, sous forme de doses unitaires, adaptée et présentée pour une première période d'administration de 3 à 36 jours, comprenant le composé de bismuth pharmaceutiquement acceptable et les premier et deuxième antibiotiques ou agents antibactériens et une deuxième composition pharmaceutique comprenant ledit suppresseur d'acide pour le traitement de l'ulcère, sous forme de doses unitaires, adaptée et présentée pour une deuxième période d'administration de 3 à 36 jours avant la partie initiale de ladite première période d'administration ou simultanément avec celle-ci.

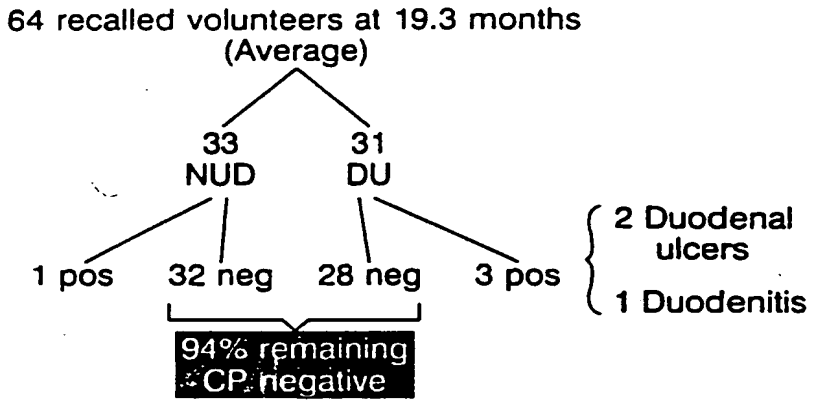

Fig. 2